REMARKS

Status of Claims

Claims 71-74, 76-117, and 119-244 were pending, and new claims 245-428 are added herewith. Claims 99, 103, 108, 112, 113, 145, 146, 155-159, 214, 218, 223, 233 and 241 are withdrawn from consideration.

Response

Applicants appreciate the indication by the Office of allowable subject matter (paragraph 14 of the Office Action) and acknowledgment by the Office that the pending method claims are free of prior art (paragraph 4 of the Office Action). The remaining rejections are addressed below. For the convenience of the Examiner, the comments below are numbered according to the paragraph numbering used in the Office Action.

¶ 1. Noted.

¶ 2. Noted. Dependent claims 112, 113, 145 and 146 are canceled in this amendment, without estoppel or prejudice to future prosecution.

¶ 3. Noted. Applicants understand that papers 37 and 39 were responsive to a requirement under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits. Applicants understand that if a generic claim is held to be allowable, Applicants will be entitled to consideration of claims to non-elected species (i.e., claims to other species which are written in dependent form or otherwise include all the limitations of an allowed generic claim) as provided by 37 C.F.R. 1.141.

¶ 4. Noted. Applicants thank the Examiner for his careful consideration of these claims and acknowledgement that the method claims are free of prior art.

¶ 5. Noted.

¶ 6. Noted.

¶ 7. Rejections under 35 U.S.C. § 112, First Paragraph (New Matter)

Claims 151, 166, 168-171, 231, and 239 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not adequately described in the specification.

A) Claim 151

The Office states "[t]here is no support in the specification . . . for the kit of claim 151 which recites "medium for cell incubation." This rejection is traversed in part and overcome in part by amendment. Claim 151 has been amended to recite "comprising a physiologically acceptable buffer." See the specification at, e.g., page 27, lines 10-14. An example of physiologically acceptable buffer is cell culture media. See the specification at, e.g., page 27, line 13. In view of the clear support in the specification for claim 151 as amended, Applicants respectfully request that this rejection be withdrawn. New claim 334 depends from claim 151, and recites that the physiologically acceptable buffer is cell culture media.

B) Claims 166, 231, and 239

The Office asserted there is no support for coupling via the biotin/avidin system, as recited in kit claims 166, 231 and 239, and that Applicants' reference in Paper 37 to page 15, lines 11-14, of the specification was inadequate because "it only discloses use of avidin biotin attached to the aforementioned specific molecules [i.e., avidin attached to a hydrophobic anchor moiety coupled to a biotin-labeled antibody]" (Office Action at page 3). Applicants respectfully traverse.

The avidin-biotin system is extremely well know to those of skill in the art. In the instant specification, the use of the avidin-biotin system for coupling an anchor to a capture moiety is described and a variety of examples are provided. Some of the examples describe the use of avidin-biotin with specific anchor and/or capture moieties, while others refer to the use of avidin-biotin with generically-described anchor and/or capture moieties. Examples described in the specification include:

- an avidin-conjugated anchor moiety (hydrophobic) and a biotin-conjugated capture moiety (antibody)[1]

[1] See the specification at, e.g., page 15, lines 11-14.

- a biotin-conjugated anchor moiety (dextran-hydrophobic) and an avidin-conjugated capture moiety (antibody)[2]

- an avidin or biotin conjugated anchor moiety (antibody) and an avidin or biotin-conjugated capture moiety (generic)[3]

- a biotin anchor moiety (conjugated to cell) and an avidin-conjugated capture moiety (antibody)[4]

- an avidin or biotin conjugated anchor moiety (generic) and an avidin or biotin-conjugated capture moiety (generic)[5]

As the Office states, the purpose of the written description requirement is to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, the applicant was in possession of the invention. The law does not require the applicant to mechanically list every possible combination of elements that can be used in a claimed invention. In the instant case, Applicants have *described* the use of the well known avidin-biotin system by describing its use with a *generic* anchor moiety and a *generic* capture moiety (both of which are discussed in detail elsewhere in the specification) as well as describing several *specific* examples of avidin-biotin based coupling of anchor and capture moieties. See the specification at, e.g., page 12, lines 24-26 and citations *supra*. Particularly when considered in view of the fact that the biotin-avidin system is one of the most common in experimental biology, this description clearly conveys the Applicants' possession of the invention in compliance with the written description requirement. Applicants respectfully maintain this rejection of claims should be withdrawn.

C) Claim 168

Claim 168 was asserted to contain new matter. The Office stated that "the only method disclosed in the specification for determining the amount of cells is the method of original claim 31 which includes additional steps not recited in claim 168." (Original claim 31 recited a step of "labeling the cells with at least one additional label" and detecting the relative amount of the two labels as part of the analysis of the cell population.)

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[2] See the specification at, e.g., page 15, lines 24-27.

[3] See the specification at, e.g., page 15, line 33 to page 16, line 2.

[4] See the specification at, e.g., page 41, lines 25-34.

[5] See the specification at, e.g., page 12, lines 24-26.

Applicants respectfully note that a method for determining the amount of cells labeled with a product in a population of cells without using a second label is supported in the specification. See, for example, Figure 11b and corresponding Example 2 (e.g., at page 44, lines 16-17). In this Figure, cells that secrete IgM are labeled and determined to be 14.2% of the total cells in the population. Thus, claim 168 is supported in the specification.

New claims 245, 246, and 247, correspond generally to pending claims 168, 170 and 171, but for additional clarity, recite that the *proportion*, rather than *amount*, of cells in a population labeled with a product(s) is determined.

¶ 8. <u>Rejections under 35 U.S.C. § 112, First Paragraph (Written Description)</u>

Claims 71-74, 76-81, 85-87, 90-98, 101, 102, 104-107, 114-117, 119-124, 128-138, 141-144, 147-154, 160-179, 183-197, 201-203, 206-213, 216, 217, 219-222, 227-232, 234-240, 242, 243, and 244 were rejected as allegedly not adequately described in the specification. The Office asserts that the "terms 'coupled' to cells or attached via a 'anchor moiety' would encompass a potentially large genus of undisclosed reagents for coupling/anchor moieties to attach the capture moiety to the cell surface."

The Office acknowledges that the specification describes a number of methods of coupling capture moieties to cells. These methods include (1) coupling involving fatty acids, (2) coupling involving antibodies, (3) coupling involving lectins, and (4) chemical coupling.[6] In addition to the methods specifically acknowledged by the Office to be described, other methods, including coupling via polycations (such as chitosan and polylysine) to negatively charged cells (see specification at, e.g., page 14, lines 3-12), use of agents that specifically bind to cell surface molecules such as MHC antigens or glycoproteins (see specification at, e.g., page 10, lines 30-32), and binding of a capture moiety that is a bispecfic antibody to the cell (see specification at, e.g., page 13, lines 21-24; also see original claim 13) are described in the specification.

As the Office notes, Section 112 requires that the specification convey with reasonable clarity that, as of the filing date, the applicant was in possession of the invention. *Vas-Cath v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). However, the Office appears to suggest

[6] The Office Action makes reference to chemical coupling "via traditional organic chemistry methods." For clarity of the record, Applicants can not know what is meant by "traditional organic chemistry methods" and, accordingly, do not acquiescence to this characterization.

that possession under this requirement can be demonstrated only by the recitation of specific molecules. Applicants respectfully submit this is not the proper standard. It is well established that, with regard to composition claims, description of each and every member of a genus is not the standard for compliance with the written description requirement. *The Regents of the University of California v Eli Lilly and Company*, 43 USPQ2d 1398 (cited at length by the Office in the instant Office Action). The *Lilly* Court held that the written description requirement is satisfied by description of a *representative number* of species in the genus. *Lilly* at 1568; see, also MPEP § 2163 et seq. According to *Lilly*, a fully described genus requires that one of ordinary skill in the art would have been able to "recognize the identity of the members of the genus." *Eli Lilly*, 119 F3d 1559, 1568. The description provided in the instant specification (including description of the species noted above) meets this standard. The ordinarily-skilled artisan reading Applicants' disclosure would recognize additional or alternative coupling methods and/or anchor moieties that are useful in the claimed methods. Taken together, the various exemplary descriptions of coupling methods and anchor moieties provided by the instant specification constitute the disclosure of a number of coupling methods and moieties fully adequate to support the terms "coupling" and "anchor moieties." In the terms used in *Lilly*, a skilled artisan would have been able to "recognize the identity" of a broad range of suitable coupling methods and anchor moieties based on the specification. Accordingly, the specification complies with the requirement for written description of the claimed invention.

Applicants also submit, respectfully, that the argument presented by Office to make this rejection is not in accord with decisions of the Court of Appeals for the Federal Circuit and thus is not proper. For example, the Office cites *Fiers v. Revel*, 25 USPQ2d 1601 (Fed. Cir. 1993) and *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016 (Fed. Cir. 1991) in support of its position, and asserts the specification is deficient because "the amino acid itself or isolated protein is required" and because "the skilled artisan cannot envision the detailed structure of the encompassed reagents" (Office Action at page 4; emphasis added). However, the application of *Fiers* and *Amgen* to the present application is inapt. *Fiers* and *Amgen* addressed the written description requirement as applied to claims to a *nucleic acid* defined only by a statement of function or result. The claims in the present case are not directed to a nucleic acid or specific proteins. The CAFC has specifically held that, consistent with Office Guidelines, the written description requirement does not necessarily require the disclosure of a chemical structure. See,

e.g., *Enzo Biochem. v. Gen-Probe*, 63 USPQ2d 1609 (Fed. Cir. 2002). Further, the CAFC has made it clear that holdings and dicta directed to *sequence* should not be extended to non-sequence inventions such as the present invention. See *Amgen Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.*, 314 F.3d 113; 2003 U.S. App. LEXIS 118; 65 USPQ2d 1385. Further, the courts have consistently noted that compliance with the written description requirement will "necessarily vary depending on the nature of the invention claimed." *Vas-Cath v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). Accordingly, any blanket application of a requirement for the description of an "amino acid sequence" or chemical formula under *Fiers* and *Amgen* to the instant invention is inappropriate.

The ordinarily-skilled practitioner would understand from the description and examples in the instant application that the Applicants had possession of the claimed invention. Accordingly, Applicants respectfully request allowance of all pending claims.

Even Using the Criteria of the Office, Newly Added Independent Claims 248-249, 251-252, 254-255, 257-258, 260-261, 263-264, 266-267, and 269-270, and Claims Dependent From Them, Comply With the Written Description Requirement

It its rejection of claims as allegedly not supported by the specification, the Office asserts "[t]he only procedures disclosed in the specification for coupling a capture moiety to a cell/anchoring moieties for attaching a capture moiety to a cell are direct chemical coupling via traditional organic chemistry methods, or use of fatty acids or antibodies or lectins." In addition, the Office stated that, *inter alia*, claims 82, 83, 84, 114, 173, 182, 198, 199, and 200 (which recite the methods of coupling acknowledged by the Office to be supported) would be allowable if rewritten in independent form. Thus, the Office has acknowledged that at least the following elements are supported in the specification:

> ". . . wherein said capture moiety is coupled to said cells through direct chemical coupling of the capture moiety to components on the cell surface, optionally through a linking moiety" *as recited in objected-to claims 84, 127, 181, and 200*;

". . . wherein said capture moiety is coupled to said cells through an anchoring moiety, and wherein the anchoring moiety is a lipid anchor" *as recited in objected-to claims 82, 125, 180, and 198*; and,

". . . wherein said capture moiety is coupled to said cells through an anchoring moiety, and wherein the anchoring moiety is an antibody, or an antigen-binding fragment thereof" *as recited in objected-to claims 83, 126, 182, and 199.*

To expedite prosecution, Applicants have added new independent claims 248, 251, 254, 257, 260, 263, 266, and 269. These claims correspond to rejected claims 71, 72, 115, 167, 168, 172, 189, and 190, respectively, but moot the sole basis of the rejection by additionally reciting that "a) said capture moiety is coupled to said cells through direct chemical coupling of the capture moiety to components on the cell surface, optionally through a linking moiety or b) said capture moiety is coupled to said cells through an anchoring moiety, and i) the anchoring moiety is a lipid anchor or ii) the anchoring moiety is an antibody, or an antigen-binding fragment thereof." As this language is acknowledged by the Office to be supported in the specification, these claims are allowable. Claims 319-321, 328-330, 340-342, 349-351, 358-360, 367-369, 376-378, and 388-390 depend from the aforelisted independent claims are also believed allowable.

To expedite prosecution, Applicants have also added new independent claims 249, 252, 255, 258, 261, 264, 267, and 270. These claims correspond to rejected claims 71, 72, 115, 167, 168, 172, 189, and 190, respectively, but moot the sole basis of the rejection by additionally recite "wherein said capture moiety is coupled to said cells through an anchoring moiety, and wherein the anchoring moiety is a lectin." As noted above, the Office has acknowledged that the procedures disclosed in the specification for coupling a capture moiety to a cell/anchoring moieties for attaching a capture moiety to a cell include use of lectins. Claims 322-324, 331-333, 343-345, 352-354, 361-363, 370-372, 379-381, and 391-393 depend from the aforelisted independent claims and are also believed allowable.

Even Using the Criteria of the Office, Newly Added Dependent Claims 272-281, and Claims Dependent From Them, Comply With the Written Description Requirement

New claims 272, 274, 276, 278, and 280 depend from claims 73, 74, 117, 173 and 191, and recite that the anchoring moiety is a lipid anchor. New claims 273, 275, 277, 279, and 281 depend from claims 73, 74, 117, 173 and 191, and recite that the anchoring moiety is an antibody, or an antigen-binding fragment thereof. Applicants respectfully submit that claims 272-281 clearly comply with the written description requirement and should be allowed.

New Claims 250, 253, 256, 259, 262, 265, 268, and 271, and Claims Dependent From Them, Comply With the Written Description Requirement

New Claims 250, 253, 256, 259, 262, 265, 268, and 271 are directed to the case in which the capture moiety is a bispecific antibody or fragment thereof bound to both the secreted product and to the cell. As noted above, binding of a capture moiety that is a bispecfic antibody to the cell is described in the specification (see, e.g., page 13, lines 21-24; also see original claim 13).

¶ 9. Noted.

¶ 10. Rejections under 35 U.S.C. § 102(a)

Claims 93-95, 101, 104, 106, 107, 109, 147-149, 209, 210, 216, 219, 221, 222, and 224 were rejected as allegedly anticipated by Kohler et al., 1980, *Eur. J. Immunol.* 10:467-76 ("Kohler"). The rejected claims are composition claims that depend, directly or indirectly, on one of the following independent claims: 71, 72, 95, 115, 149, 210, and 190 (as a product of the process of claim 190). Applicants respectfully traverse the rejection.

Kohler Described A "Suicide Selection Procedure"

The Kohler et al. article describes a "suicide selection procedure" (see Kohler at page 474, column 2). In this procedure, TNP was coupled to hybridoma clones, some of which secreted antibodies that bound the coupled TNP. Kohler described plaque assays in which those clones are incubated with specific anti-mouse-μ serum for the purpose of, and under conditions in which, the antibody-secreting cells are lysed (see Kohler at page 468, § 2.3).

Kohler Did Not Teach Or Suggest A Composition Containing Viable Cells Labeled With A Label Moiety

The claimed invention is directed to compositions of cells labeled with secreted product (e.g., see claims 95 and 210). Implicitly in the term "cell," and explicitly in other phrases recited in the rejected claims (i.e., "in which cells are not lysed", "positively identified", "positively selected") the claimed compositions comprise viable cells that are not lysed.[7] In contrast, the compositions described by Kohler, in which cells are combined with anti-mouse-μ serum, contains lysed cellular material. The heart of Kohler's method is use of complement-containing serum for the purpose of **lysing** the cells, thereby allowing culture of hybridoma clones secreting nonfunctional antibodies. Kohler's compositions are distinct from, and do not anticipate, the present invention.

Because Kohler did not teach a composition in which cells are not lysed (i.e., a composition comprising viable cells), the reference does not include all of the elements of the present claims, and thus cannot anticipate the claimed compositions.

For increased clarity, Applicants have added new independent claims 399 and 404. These claims correspond generally to claims 149 and 210 but recite that the claimed composition comprises *viable* cells. Although the word "viable" is not recited *ipsis verbis* in the specification, *ipsis verbis* recitation is not required. *Vas-Cath Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111, 1116-1117 (Fed. Cir. 1991); *In re Alton* 37 USPQ2d 1578, 1584 (Fed. Cir. 1996)). The disclosure need only reasonably convey to persons skilled in the art that the inventor had

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[7] See the following phrases in the rejected claims or claims from which the rejected claims depend:

Claim 71. " . . . wherein said cells are **not lysed** during said method."

Claim 72. " . . . wherein said cells are **not lysed** during said method."

Claim 95. "A composition comprising **cells positively identified** based on a product secreted by said cells . . . "

Claim 115. " . . . wherein said cells are **not lysed** by said method . . . **positively separating said cells** labeled with said product

Claim 149. "A composition comprising **cells positively identified** based on a product secreted by said cells . . . "

Claim 190. " . . . wherein said cells are **not lysed** by said method . . ."

Claim 210. "A composition comprising **cells** labeled with a product . . . "

possession of the claimed invention. In the present case, Applicants' possession of the invention is indisputable. See, for example, page 29, lines 3-5 of the specification ("purpose of this example was to separate living cells"); page 5, lines 9-10 ("labeled cells are not lysed as part of the separation procedure"); and page 39, lines 10-14 (". . . the cells could not be labeled with propidium iodide, a dye that selectively labels dead cells, and could again be cultured.").

Because Kohler did not teach a composition in which cells are not lysed (i.e., a composition comprising viable cells), the reference does not include all of the elements of the present claims, and thus cannot anticipate the claimed compositions.

New claims 400-403, and 405-415, depend from claims 399 and 404 (discussed above) and further describe the nature of the coupling of the capture moiety to the cell (as also discussed in ¶ 8). New claims 414-428 depend from claims 399 to 413 and recite that the product is a cytokine.

Kohler Did Not Teach Or Suggest A Composition In Which The Secreted Product Is Labeled With A Detectable Label Moiety

New claims 404-415 further describes the nature of the label moiety of the claimed compositions. Claim 404 recites that the cell-bound secreted product is labeled with a label moiety that permits the labeled cells to be positively selected based on the presence of said label moiety. Examples of label moieties that permit the labeled cells to be positively selected include those with labeling materials such as fluorophores, radioactive isotopes, chromophores and magnetic particles (see the specification at, e.g., page 4, lines 21-26). See, e.g., claims 411 to 413. Support for cell-bound secreted product is labeled with a label moiety that permits the labeled cells to be positively selected based on the presence of said label moiety is replete in the specification (see, e.g., the Examples). In contrast, the secreted product in Kohler (i.e., anti-TNP IgM) is not labeled with a label moiety that permits the labeled cells to be positively selected based on the presence of said label moiety.

Because Kohler did not teach a composition in which cells are not lysed (i.e., a composition comprising viable cells) labeled with a label moiety that permits the labeled cells to be positively selected, the reference does not include all of the elements of the present claims, and thus cannot anticipate the claimed compositions.

¶ 11. Noted.

¶ 12 Rejections Under 35 U.S.C. § 103

Claims 93-98, 100-102, 104-107, 109-111, 147-149, 209-213, 215-217, 219-222, and 224-226 were rejected as allegedly obvious in view of Kohler et al., 1980, *Eur. J. Immunol.* 10:467-76 and Segal (U.S. patent 4,676,980) and Brennan et al., 1985, *Science* 229:81-83 ("Brennen").

The Cited References

Kohler is discussed above in ¶10.

Segal and **Brennen** are relied on by the Office for describing bispecific antibodies.

Segal is cited by the Office for describing "that bispecific antibodies can bind a cell surface antigen on the surface of a target cell and also bind another desired antigen." More specifically, however, Segal describes a method in which cross-linked antibody heteroaggregates link a surface molecule on a cytotoxic cell and a surface molecule on a target cell to be lysed by the cytotoxic cell. See Segal at column 1, lines 45-60. Segal does not describe or suggest use of a bispecific antibody to capture a product secreted by a cell.

Brennen is cited by the Office for describing use of bispecific antibodies "to link two different molecules." Brennen described a novel method for making bispecific antibodies, and described use of bispecific antibodies to immobilize an enzyme (or a pair of enzymes) to a cellulose substrate. Brennan stated "this illustrates the potential use of bispecific antibodies for the highly specific colocalization of multiple enzymes." See Brennen at page 83, paragraph bridging first and second columns. Brennen did not describe or suggest use of a bispecific antibody to capture a product secreted by a cell.

Brennen is also cited by the Office as teaching "the use of bispecific antibodies in immunoassays (see page 81, column 2)." It is not clear to applicants what the Office intends to be encompassed by the term "immunoassays." As used in the biosciences and biomedical art, the term "immunoassay" is a rather general term and does not refer to any specific assay. The uses of bispecific antibodies cited by Brennen at page 81 are *immunodiagnostic* procedures and *targeted delivery* of drugs. Neither of these is relevant to the present invention and neither supports the position set forth in the Office Action.

The Office Has Failed to Establish Prima Facie Obviousness

As described in detail below, the Office has not established a *prima facie* case of obviousness. To establish *prima facie* obviousness, the Office must indicate where the prior art provides reason or motivation for one of skill to make the claimed composition or carry out the claimed method. The Office must also demonstrate that one of ordinary skill would have had a reasonable expectation of success in attempting to make the composition or carry out the method. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). In determining obviousness the reference must be read without benefit of applicants' teachings.

The Office Has Not Even Asserted The Prior Art Provided A Suggestion To Modify Kohler To Result In The Compositions of Claims 93, 94, 95, 101, 104, 106, 107, 109, 147, 148, 149, 209, 210, 216, 219, 221, 222, and 224

Although claims 93, 94, 95, 101, 104, 106, 107, 109, 147, 148, 149, 209, 210, 216, 219, 221, 222, and 224 stand rejected as allegedly obvious under § 103, the Office has set forth **no** arguments to support the assertion of obviousness, i.e., **no** argument or evidence as to why one of ordinary skill in the art would modify the compositions described by Kohler to result in the present invention. Thus, it appears that the Office's basis for this rejection is the same as that set forth in rejecting the same claims as allegedly anticipated. Accordingly, Applicants traverse this rejection and refer to and reiterate the comments in ¶10, *supra*. New claims 399-428 are also not obvious, for the same reasons explained in the traverse of the anticipation rejection set forth in ¶ 10.[8]

The Invention As Claimed in Claims 96, 97, 98, 100, 102, 105, 110, 111, 211, 212, 213, 215, 217, 220, 225, and 226 Was Not Obvious In View of The Cited References

Claims 96, 97, 98, 100, 102, 105, 110, 111, 211, 212, 213, 215, 217, 220, 225, and 226 were also rejected as allegedly obvious in view of Kohler, Segal and Brennan. These claims

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[8] For completeness, Applicants note the following: Nothing in the Segal or Brennan references, taken together in combination with Kohler, renders any claim obvious. With regard to the description in of bispecific antibodies in Segal and Brennan, the rejected claims do not recite a bispecific antibody.

relate to, *inter alia*:

a) a fluorochromated label moiety (claims 102/217);

b) a capture moiety coupled to cells through an anchoring moiety (claims 96/211);

c) a capture moiety that is an antibody or antigen-binding fragment thereof (claims 97/212) or is a bispecific antibody (claims 98/213);

d) an anchoring moiety that is an antibody or an antigen-binding fragment thereof (claims 100/215);

e) a product is a IFNγ, IL1, IL2, IL4, IL10, IL12, TGFβ, TNF, GMCSF, and SCF. (claims 105/220); or,

f) a linking moiety that includes branched polymers such as dextran (claims 110/111//225/226).

However, the basic premise underlying the position of the Office is incorrect. The case for obviousness set forth by the Office is premised on the Office's assertion ". . . Kohler et al teach the claimed invention except for [use of a bispecific antibody . . .]" As explained in ¶ 10, *supra*, this underlying premise is incorrect.

Furthermore, Claims 102 and 217, Reciting "Wherein The Label Moiety Is Fluorochromated" Were Not Obvious

In articulating its obviousness rejection, the Office states categorically "[u]se of fluorescinated antibodies in immunoassays is well known in the art." Applicants respectfully submit that whether or not the use of fluorescinated antibodies in "immunoassays" (by which Applicants assume the Office means assays such as RIA or ELISA) is routine is not material. The relevant question is whether or not the cited references suggest modification of the Kohler assay to arrive at Applicants' invention. First, Applicants submit Kohler does not teach an "immunoassay." Kohler describes a method for *cloning* by suicide selection. There was no motivation to "modify" the Kohler method to produce cells labeled with fluorescinated antibodies because these antibodies would not have been useful for suicide selection. The Office is respectfully reminded that the motivation to modify the Kohler compositions must be provided by the cited references, not by Applicants own disclosure.

Furthermore, The Remaining Claims, Reciting Elements (b) – (f), Above, Were Not Obvious

The Office states that Segal teaches that bispecific antibodies can be used to bring an antigen to a cell. As noted above, Segal, describes a method for causing lysis of cells to which the bispecific antibody is bound.

The Office further asserts a "routiner **would [have]** used bispecific antibodies which bind any art known molecule that exists on the surface of a desired target cell. A routiner **would have** used any desired capturing probe instead of TNP, including an antibody and **would have** attached the antibody to the cell surface using any art known procedure including those utilizing linking agents . . . [and] . . . a **routiner would have** created cells which bound any particular secreted molecule (such as IFN-γ)." Mere assertions by the Office, unsupported by the cited references, of what a routiner "would have" done are not sufficient to establish *prima facie* obviousness. The Office must, at minimum, explain why the ordinarily skilled practitioner would have been motivated by the cited references to make the claimed invention, and why the practitioner would have had a reasonable expectation of success. Simply noting it would have been *possible* to pick and choose elements from the prior art descriptions that could theoretically, and with benefit of Applicants disclosure, lead to a particular composition, does not establish obviousness.

Further, neither Segal nor Brennen (or the combination) remedy, by virtue of describing bispecific antibodies, the deficiencies of the Kohler reference.

¶ 13 Rejections Under 35 U.S.C. § 103

Claims 150-154, 160-166, 227-232, 234-240, 242 and 243 stand rejected as allegedly obvious in view of Kohler, Segal, Brennen (all discussed above) and Zuk et al. (U.S. Pat. No. 4,281,061) ("Zuk").

Zuk is cited as teaching that reagents for immunoassay can be provided as kits. Zuk, of course, does not describe or suggest either the kits of the present invention or their components. Further, Kohler, Segal, Brennen, and Zuk, taken together do not describe or suggest either the kits of the present invention or their contents, for reasons discussed *supra*.

¶ 14. Claim Objections

Claims 82-84, 88, 89, 125-127, 139, 140, 180-182, 198-200, 204, and 205 were objected to. The Office indicated the claims would be allowable if rewritten in independent form. To expedite prosecution, claims 82, 83, 84, 114, 173, 182, 198, 199, and 200 (from which the remaining claims depend) have been amended as requested by the Office. As discussed *supra* Applicants maintain the objected-to claims were patentable in their original form.

Additional New Claims

New claims 282-285; 286-287; 288-289; and 290-294 depend from claims 167, 168, 169, and 179, respectively and recite, *inter alia*, that the capture moiety is an antibody or antigen binding fragment thereof. The claims add no new matter.

New claims 295-297; 298-300; 301-303; 304-306; 307-309; 310-312; 313-315; 316-318; 325-327; 337-339; 346-348; 355-357; 364-361; 373-375; 382-384; and 394-396 depend from claims 71, 72, 115, 167, 168, 172, 189, 190, 250, 253, 256, 259, 262, 265, 268, and 272 respectively and recite, *inter alia*, that the label moiety is an antibody specific for the product. The claims add no new matter.

Relationship of Species Election to New Claims

In the Response to Restriction Requirement mailed July 16, 2001, Applicants elected the label moiety species "fluorochromated"; the anchoring moiety species "antibody"; the product species "cytokine"; the cytokine "IFN-γ"; the branched polymer species "dextran molecules"; and the cell surface marker "CD45" (see Papers 37 and 39). New claims 245-428 have been added in this amendment. Applicants believe claims 245-249, 250-251, 253-254, 256-257, 259-260, 262-263, 265-266, 268-269, 271, 273, 275, 277, 279, 281-283, 285-287, 289-292, 294-296, 298-299, 301-302, 304-305, 307-308, 310-311, 313-314, 316-317, 319-320, 325-326, 328-329, 334-335, 337-338, 340-341, 346-347, 349-350, 355-356, 358-359, 364-365, 367-368, 370-371, 373-374, 376-377, 382-383, 385-389, 399-400, 402-405, 407-415, 417-420, and 422-428 read on

the species elected for examination. As amended, claims 82, 84, 182, 198, 200 recite an anchoring moiety species other than elected species "antibody."[9]

CONCLUSION

If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

Applicants respectfully request an interview with the Office prior to issuance of a further substantive Office Action in this application.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 212302000320.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

Dated: October 22, 2003

By: _____

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[9] Claims 82, 84, 198, and 200 were indicated by the Office to be allowable if rewritten (as they have been) in independent form.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

DIRECT SELECTION OF CELLS BY SECRETION PRODUCT

In the Claims:

82. (Amended) [The method of claim 73] A method to positively identify cells based on a product secreted by the cells, comprising culturing said cells under conditions wherein the product is secreted and bound to a capture moiety coupled to said cells, wherein said capture moiety specifically binds the product, thereby labeling cells with said product, wherein said product is labeled with a label moiety, wherein said cells are not lysed during said method, wherein said capture moiety is coupled to said cells through an anchoring moiety, and wherein the anchoring moiety is a lipid anchor.

83. (Amended) [The method of claim 73] A method to positively identify cells based on a product secreted by the cells, comprising culturing said cells under conditions wherein the product is secreted and bound to a capture moiety coupled to said cells, wherein said capture moiety specifically binds the product, thereby labeling cells with said product, wherein said product is labeled with a label moiety, wherein said cells are not lysed during said method, wherein said capture moiety is coupled to said cells through an anchoring moiety, and wherein the anchoring moiety is an antibody, or an antigen-binding fragment thereof.

84. (Amended) [The method of claim 71] A method to positively identify cells based on a product secreted by the cells, comprising culturing said cells under conditions wherein the product is secreted and bound to a capture moiety coupled to said cells, wherein said capture moiety specifically binds the product, thereby labeling cells with said product, wherein said product is labeled with a label moiety, wherein said cells are not lysed during said method, and wherein said capture moiety is coupled to said cells through direct chemical coupling of the capture moiety to components on the cell surface, optionally through a linking moiety.

114. (2x Amended) [The method of claim 71] A method to positively identify cells based on a product secreted by the cells, comprising culturing said cells under conditions

wherein the product is secreted and bound to a capture moiety coupled to said cells, wherein said capture moiety specifically binds the product, thereby labeling cells with said product, and wherein said product is labeled with a label moiety, wherein said cells are not lysed during said method further comprising the step of positively separating said cells labeled with said product secreted by said cells, and wherein said product is labeled with a label moiety.

151. (Amended) The kit of claim 150 further comprising a physiologically acceptable buffer [medium for cell incubation].

173. (Amended) [The method of claim 172] A method to positively separate cells based on a product secreted by the cells comprising separating cells labeled with the product, wherein said cells have been coupled to a capture moiety that specifically binds a product secreted by said cells and wherein said cells have been cultured under conditions wherein the product is secreted and bound to said capture moiety, thereby producing cells labeled with said product, wherein said cells are not lysed by said method, [and] wherein said product is labeled with a label moiety, and wherein said capture moiety is coupled to said cells through an anchoring moiety.

182. (Amended) [The method of claim 172] A method to positively separate cells based on a product secreted by the cells comprising separating cells labeled with the product, wherein said cells have been coupled to a capture moiety that specifically binds a product secreted by said cells and wherein said cells have been cultured under conditions wherein the product is secreted and bound to said capture moiety, thereby producing cells labeled with said product, wherein said cells are not lysed by said method wherein said product is labeled with a label moiety, and wherein said capture moiety is coupled to said cells through direct chemical coupling of the capture moiety to components on the cell surface, optionally through a linking moiety.

198. (Amended) [The method of claim 191] A method to label cells with a product secreted by the cells, comprising culturing said cells under conditions wherein the product is secreted and bound to a capture moiety coupled to said cells, wherein said capture moiety specifically binds the product, thereby labeling cells with said product, wherein said product is optionally labeled with a label moiety, wherein said cells are not lysed during said method,

wherein said capture moiety is coupled to said cells through an anchoring moiety, and wherein the anchoring moiety is a lipid anchor.

199. (Amended). [The method of claim 191] A method to label cells with a product secreted by the cells, comprising culturing said cells under conditions wherein the product is secreted and bound to a capture moiety coupled to said cells, wherein said capture moiety specifically binds the product, thereby labeling cells with said product, wherein said product is optionally labeled with a label moiety, wherein said cells are not lysed during said method, wherein said capture moiety is coupled to said cells through an anchoring moiety, and wherein the anchoring moiety is an antibody, or an antigen-binding fragment thereof.

200. (Amended) [The method of claim 190] A method to label cells with a product secreted by the cells, comprising culturing said cells under conditions wherein the product is secreted and bound to a capture moiety coupled to said cells, wherein said capture moiety specifically binds the product, thereby labeling cells with said product, wherein said product is optionally labeled with a label moiety, wherein said cells are not lysed during said method, and wherein said capture moiety is coupled to said cells through direct chemical coupling of the capture moiety to components on the cell surface, optionally through a linking moiety.

Please add new claims 245-428.